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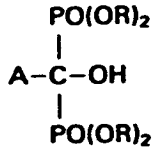
(71) Applicants
Schering AG.,
(FR Germany),
Berlin and Bergkamen,
Federal Republic of
Germany.
(72) Inventors
Dr. Helmut Biere,
Dr. Clemens Rufer,
Dr. Irmgard Bottcher.
(74) Agent and/or Address for
Service
Abel and Imray,
Northumberland House,
303-306 High Holborn,
London WC1V 7LH.

(54) Diphosphonic acid derivatives, process for their preparation and pharmaceutical preparations containing them

(57) Diphosphonic acid derivatives of the general formula



(I),

in which
R is hydrogen or (C_{1-4}) alkyl and
A is the radical of an anti-inflammatorily and anti-phlogistically active carboxylic acid, ACOOH, which contains an aryl or heteroaryl group, processes for their preparation and their use as anti-inflammatory and anti-arthritic agents.

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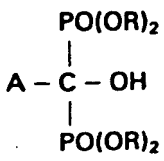
Certain of the Chemical formula(e) appearing in the printed specification were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.
This print takes account of replacement docments later filed to enable the application to comply with the formal requirements of the Patents Rules 1982.

SPECIFICATION

Diphosphonic acid derivatives, process for their preparation and pharmaceutical preparations containing them

The invention relates to diphosphoric acid derivatives, processes for their preparation and to pharmaceutical preparations that contain these compounds as active substances.

The present invention provides a diphosphonic acid derivative of the general formula



(I)

in which

R represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms, each R present being the same or different, and

A represents the radical of an anti-inflammatorily and anti-phlogistically active carboxylic acid, ACOOH, which contains an aryl or heteroaryl group.

Suitable ester derivatives of the diphosphonic acid of the invention are methyl and ethyl esters.

It is possible for each radical represented by R in a compound of the invention to be the same or different. However, generally it is preferred that each radical R is the same.

The present invention also provides a salt, especially a physiologically tolerable salt, of a compound of the invention. Suitable salts are alkali metal and alkaline earth salts, especially the sodium salts.

A salt or an ester of a diphosphonic acid of the invention may be formed at any or all of the salt-forming or ester-forming groups present, for example at the acid and hydroxy groups present. Usually where two or more salt groups or two or more ester groups are present in a compound of the invention, the salt groups will all be the same and the ester groups will ail be the same.

Preferred phosphonic acid derivatives of the invention may be derived from anti-inflammatorily and anti-phlogistically active carboxylic acids generally known for their anti-inflammatory action, for example, ibuprofen, butibufen, MK 830, flurbiprofen, alclofenac, pirprofen, ketoprofen, fenoprofen, fenclofenac and diclofenac. Structurally similar carboxylic acids having a good anti-inflammatory action that are also suitable for the manufacture of diphosphonic acid derivatives of the invention are, for example, cliprofen, suprofen and indoprofen.

Further preferred compounds of the invention may be derived from carboxylic acids that are also distinguished by a good anti-inflammatory and anti-phlogistic action, for example, BL 2365, clidanac and 6-chloro-5-cyclopentylmethyl-1-indanecarboxylic acid.

Other preferred compounds of the invention may be based on, for example, the compounds benoxaprofen, cicloprofen, naproxen and isoxepac, which also have a good action. Similar carboxylic acids having a good action that are also suitable for the manufacture of diphosphonic acid derivatives of the invention are carprofen and metiazinic acid.

Also preferred as starting materials for the preparation of diphosphonic acid derivatives of the invention are, for example, trifezolac, pirazolac, or lonazolac. Structurally similar phosphonic acid derivatives of the invention may be prepared from the anti-inflammatorily and anti-phlogistically active carboxylic acids, bufezolac and isofezolac, for example.

Similarly preferred compounds of the invention may be derived, for example, from carboxylic acids having good action such as indomethacin or cinmethacin.

Further carboxylic acids having a good action that are also suitable for the preparation of phosphonic acid derivatives of the invention are, for example, tiaprofenic acid, zomepirac, tolmetin, clopirac, fenclozic acid, fentiazac and sulindac.

The compounds according to the invention have a pronounced anti-inflammatory and anti-arthritic action. They are distinguished from the anti-inflammatory and anti-arthritic acids ACOOH by the fact that they are capable, *inter alia*, of influencing the synthesis and degaradation activity of bone cells (osteoblasts/ osteoclasts) in such a manner that curative effects can clearly be detected in rats with induced arthritis.

This anti-arthritic activity of the compounds according to the invention constitutes the basis for a therapy for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other related disorders, especially those of the collagen and of the skeletal system (osteoporosis, Paget's disease). In addition, as good complex formers for calcium, the phosphonates may be used in therapeutically effective manner wherever a disturbed calcium-metabolism has been found to be the cause of a disorder, for example in the case of cardiovascular disorders, ectopic calcification, etc..

The compounds may be employed in the form of their esters and semiesters, but are preferably employed in the form of the free phosphonic acids or of their physiologically tolerable salts with alkali metal hydroxides or alkaline earth metal hydroxides or tolerable organic bases.

The present invention further provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

Preferably, a pharmaceutical perparation of the invention is in unit dosage form. Also the preparation is usually in a form suitable for enteral administration, for example oral administration, or parenteral administration, for example intra-articular administration or local administration.

A pharmaceutical preparation of the invention may be a solid or liquid based formulation and, in addition to the active ingredient, may contain the usual carriers, excipients and auxiliaries, for example talc, starch, taste correctives and flavourings for tablet forms, pH regulators and isotonicity imparting substances for infusion and injection solutions.

Suitable galenical formulations are capsules, tablets, dragées and suppositories, also injection and infusion solutions and dermal preparations. Local application for treating dermal or systemic disorders is also possible.

A suitable dosage range for a pharmaceutical preparation of the invention is any normally used or recommended for anti inflammatories and anti-arthritic agents, for example a dosage range of from 1 mg to 10 g, suitably from 1 to 250 mg, of active ingredient per unit dose.

The present invention also provides a process for the preparation of a compound of the invention which comprises reacting an acyl phosphonate of the general formula

$$A-COPO(OR)_2 \qquad (II),$$

in which R and A are defined above, in the presence of a base with a phosphite of the general formula

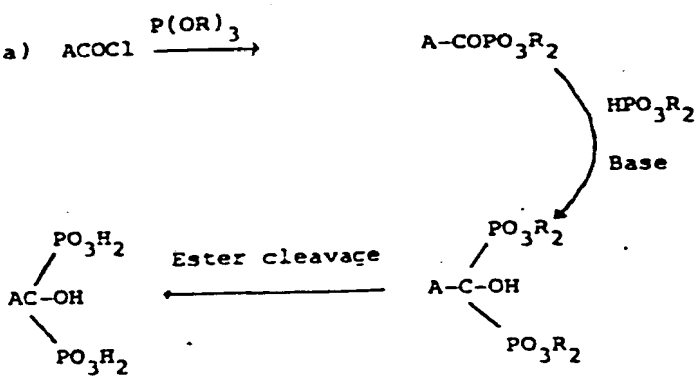
$$HPO(OR)_2 \qquad (III),$$

in which R is as defined above, and, if desired, one or more of the following reactions are carried out in any appropriate order:

i) an ester is hydrolysed or converted into another ester;
ii) an acid or base is esterified
iii) a salt is converted into an acid or base or into another salt;
iv) an acid or base is converted into a salt.

The phosphonates may be prepared according to methods which are well known to a person skilled in the art (Houben-Weyl, Methoden der organischen Chemie, Georg Thieme Verlag, Stuttgart, 4th edition, 1963 Volume XII/1,453 ff) for example as shown in the following reaction scheme

Reaction Scheme



There may be mentioned as examples of bases suitable for carrying out a process according to the invention, secondary amines, for example diethylamine, dipropylamine, diisopropylamine, morpholine and piperidine. The reaction may be carried out in an inert organic solvent, e.g. ether (for example diethyl ether, diisopropyl ether, dioxane, tetrahydrofuran) and chlorinated hydrocarbon (for example dichloromethane, tetrachloroethane, chloroform and carbon tetrachloride).

The optional subsequent hydrolysis of an ester may be carried out using a mineral acid (for example semi-concentrated hydrochloric acid or sulphuric acid). The cleavage may be achieved especially gently in an inert solvent (for example one of the above-mentioned chlorinated hydrocarbons) with trimethylsilyl

iodide. To form a salt, a free acid may be reacted in customary manner with a corresponding base.

A starting material of the general formula II required for the process according to the invention may be prepared from a corresponding acid chloride by reaction with a bis- or di-alkyl phosphite of the general formula III.

The following Examples illustrate the invention.

Example 1

A suspension of 3.70 g of 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethenephosphonic acid dimethyl ester (US Patent Specification No. 4 014 997) in 20 ml of tetrahydrofuran is added at −7°C to a solution of 1.08 g of dimethylphosphite and 0.63 g of diethylamine and the mixture is left to stand for 3 hours at −7°C and then for 16 hours at −15°C. The precipitate is then suction-filtered and in this manner 3.2 g of 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) are obtained having a melting point of 163°C.

Example 2

16.6 g of 2-(6-methoxy-2-naphthyl)-propionic acid in 200 ml of diethyl ether are stirred for 60 minutes at 20°C with 16.2 g of phosphorus pentachloride. The mixture is then concentrated, the residue is triturated with benzine and in this manner 18 g of 2-(6-methoxy-2-naphthyl)-propionyl chloride are obtained having a melting point of 95°C.

3.99 g of trimethyl phosphite are added at 20°C to 6.66 g of that acid chloride in 100 ml of diethyl ether and the mixture is left for 16 hours. The mixture is then concentrated, the residue is crystallised from diisopropyl ether and 3.63 g of 2-(6-methoxy-2-naphthyl)-propionyl-phosphonic acid dimethyl ester are obtained having a melting point of 59°C.

1.42 g of dimethyl phosphite and, at −10°C, 0.26 g of dibutylamine in 10 ml of diethyl ether are added to a suspension of 5.0 g of that phosphonic acid ester in 70 ml of diethyl ether. The mixture is cooled for 2 hours at −5°C, the product of crystallisation is suction-filtered and 4.46 g of 2-(6-methoxy-2-naphthyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) are obtained having a melting point of 140°C.

Example 3

4.66 g of 2-(4-isobutylphenyl)-propionic acid in 150 ml of diethyl ether are stirred at 20°C for an hour with 5.04 g of phosphorus pentachloride. The mixture is then concentrated *in vacuo* and 5.02 g of 2-(4-isobutylphenyl)-propionyl chloride are obtained. This is reacted as described in Example 2 with trimethyl phosphite and 2-(4-isobutylphenyl)-propionylphosphonic acid dimethyl ester is obtained. The dimethyl ester is reacted under the conditions described in Example 2 with dimethyl phosphite and 2-(4-isobutylphenyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) is obtained.

Example 4

2.68 g of 1(11-oxo-2-dibenz[*b,f*]oxepinyl)-acetic acid are dissolved in 9.15 ml of thionyl chloride and the mixture is refluxed for 3 hours. The mixture is then concentrated *in vacuo* and 3.04 g of (11-oxo-2-dibenz[*b,f*]oxepinyl)-acetyl chloride are obtained. This acid chloride is reacted under the conditions of Example 2 with trimethyl phosphite and 1.34 g of 2-(11-oxo-2-dibenz[*b,f*]oxepinyl)-1-hydroxyethene-phosphonic acid dimethyl ester are obtained having a melting point of 118°C. The product obtained is reacted as described in Example 1 with dimethyl phosphite and 2-(11-oxo-2-dibenz[*b,f*]oxepinyl)-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) is obtained having a melting point of 133°C.

Example 5

3.22 g of 6-chloro-5-cyclopentylmethyl-1-indanecarboxylic acid are refluxed for one hour together with 10.5 ml of thionyl chloride, the mixture is concentrated and 3.45 g of 6-chloro-5-cyclopentylmethyl-1-indanecarboxylic acid chloride are obtained in the form of an oil. The acid chloride is reacted as described in Example 2 with triethyl phosphite and 3 g of (6-chloro-5-cyclopentylmethyl-1-indanylidene)-hydroxymethanephosphonic acid diethyl ester are obtained having a melting point of 126°C. The compound obtained is reacted under the conditions mentioned in Example 2 with diethyl phosphite and (6-chloro-5-cyclopentylmethyl-1-indanyl)-hydroxymethane-bis(phosphonic acid diethyl ester) is obtained.

Example 6

2-[N-acetyl-N-(2,6-dichlorophenyl)-amino]-phenylacetic acid is reacted with phosphorus pentachloride in diethyl ether to form 2-[N-acetyl-N-(2,6-dichlorophenyl)-amino]-phenylacetic acid chloride. The acid chloride is then reacted under the conditions described in Example 2 with trimethyl phosphite to form 2-{2-[N-acetyl-N-(2,6-dichlorophenyl)-amino]-phenyl}-1-hydroxyethene-1-phosphonic acid dimethyl ester which is converted under the conditions of Example 1 into 2-[2-(2,6-dichlorophenylamino)-phenyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) with dimethyl phosphite.

Example 7

2-[2-(2,6-dichlorophenylamino)-phenyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) is heated with concentrated hydrochloric acid on a steam bath for 4 hours and then the mixture is diluted with

water, left to cool and the precipitated product is suction-filtered. In this manner 2-[2-(2,6-dichlorophenylamino)-phenyl]-1-hydroxyethane-1,1-diphosphonic acid is obtained.

Example 8

2.29 ml of iodotrimethylsilane are added at −5°C to 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) (2.18 g) in 15 ml of tetrachloromethane and the mixture is left at 0°C for 4 hours. The mixture is then concentrated *in vacuo* and ice-water is added. The precipitate is triturated with acetonitrile, suction-filtered and 1.92 g of 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethane-1,1-diphosphonic acid are obtained having a melting point of 202°C.

Example 9

2-(6-methoxy-2-naphthyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) is hydrolysed under the conditions of Example 7 and 2-(6-methoxy-2-naphthyl)-1-hydroxypropane-1,1-diphosphonic acid is obtained having a melting point of 205°C.

Example 10

2-(4-isobutylphenyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) is hydrolysed under the conditions of Example 7 and 2-(4-isobutylphenyl)-1-hydroxypropane-1,1-diphosphonic acid is obtained.

Example 11

2-(11-oxo-2-dibenz[*b,f*]oxepinyl)-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) is reacted under the conditions of Example 7 and 2-(11-oxo-2-dibenz[*b,f*]oxepinyl)-1-hydroxyethane-1,1-diphosphonic acid is obtained having a melting point of 228°C.

Example 12

(6-chloro-5-cyclopentylmethyl-1-indanyl)-hydroxymethane-bis(phosphonic acid diethyl ester) is reacted under the conditions of Example 7 and (6-chloro-5-cyclopentylmethyl-1-indanyl)-hydroxymethanediphosphonic acid is obtained.

Example 13

16.5 g of 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazoleacetic acid in 400 ml of diethyl ether are cooled to −15°C and 14.6 g of phosphorus pentachloride are added in portions. The mixture is stirred for 2.5 hours at −15°C and for a further 2.5 hours at 0°C. The clear solution is then concentrated *in vacuo* to a considerable extent, the oily residue is stirred with benzine (boiling range 40-60°C) and 16 g of 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazoleacetic acid chloride are obtained having a melting point of 93-95°C.

A solution of 17.5 g of 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazoleacetic acid chloride in 100 ml of tetrahydrofuran is cooled to 10°C and 9.8 ml of triethyl phosphite are added. The solution is stirred for 3 hours at 10-15°C, concentrated *in vacuo* and the oily residue is crystallised from diisopropyl ether. 18.8 g (83.4%) of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethenephosphonic acid diethyl ester are obtained having a melting point of 96-98°C.

Example 14

A solution of 18 g of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethenephosphonic acid diethyl ester in 40 ml of tetrahydrofuran is added dropwise at 0°C to a solution of 5.7 g of diethyl phosphite and 4.6 ml of diethylamine in 30 ml of tetrahydrofuran and the mixture is stirred for 5 hours at 0-5°C. The mixture is concentrated *in vacuo*, the residue is crystallised from diethyl ether and then recrystallised from carbon tetrachloride and 15.2 g (64.4 %) of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid diethyl ester) are obtained having a melting point of 141-142°C.

Example 15

11.8 g of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid diethyl ester) are stirred for 1 hour at room temperature under nitrogen with 5 equivalents of iodotrimethylsilane in 50 ml of carbon tetrachloride. The mixture is concentrated *in vacuo*, water and acetone are added to the residue, the mixture is stirred for 30 minutes and the precipitated product is recrystallised from ethanol. In this manner, 8.0 g (84 %) of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic acid are obtained having a melting point of 202-204°C.

Example 16

4 ml of 63 % hydrobromic acid are added to 0.59 g of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid diethyl ester) and the mixture is heated at 100°C for two hours. The mixture is then diluted with water and left to cool. The resulting crude product is comminuted, recrystallised from ethanol and 0.37 g (77%) of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic acid is obtained having a melting point of 201-203°C.

Example 17

A solution of 0.8 g of sodium bicarbonate in 10 ml of water is added to a solution of 1.9 g of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic acid in 5 ml of dimethylformamide and the mixture is stirred for two hours at room temperature. The precipitated product is suction-filtered, washed with a little water, dried at 110°C and 1.6 g (76%) of the disodium salt of 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane diphosphonic acid are obtained having a melting point of above 300°C.

Example 18

[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-acetylchloride is reacted as described in Example 13 with trimethyl phosphite, the mixture is worked up and 2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethanephosphonic acid dimethyl ester having a melting point of 174°C (diethyl ether) is obtained in an 80 % yield.

Example 19

2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethenephosphonic acid dimethyl ester is reacted as described in Example 14 with dimethyl phosphite, the mixture is worked up and 2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) having a melting point of 130°C is obtained in a 69% yield.

Example 20

2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) is reacted as described in Example 15, the mixture is worked up and 2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic acid having a melting point of 199°C is obtained in a 78% yield.

Example 21

a) 2.8 g of malonic acid dimethyl ester are added at 20°C to a suspension of 0.7 g of 80% sodium hydride in 40 ml of 1,2-dimethoxyethane and the mixture is stirred for 30 minutes. A solution of 7.3 g of 3-bromomethyl-4-(4-chlorophenyl)-1-(4-fluorophenyl)-pyrazole in 30 ml of 1,2-dimethoxyethane is then added and the mixture is stirred for a further 12 hours. The reaction mixture is worked up in customary manner, the residue is recrystallised from cyclohexane and 4.2 g of [4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolylmethyl]-malonic acid dimethyl ester are obtained having a melting point of 123°C.

b) 12 ml of 2N aqueous sodium hydroxide solution are added to a solution of 0.9 g of [4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolylmethyl]-malonic acid dimethyl ester in 2.5 ml of ethanol and the mixture is refluxed for 3 hours. The mixture is left to cool, acidified with 2N hydrochloric acid, the precipitate is recrystallised from acetonitrile and 0.8 g of [4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolylmethyl]-malonic acid is obtained having a melting point of 188°C.

c) A solution of 3 g of [4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolylmethyl]-malonic acid in 50 ml of chlorobenzene is refluxed until the gas development has finished (approximately 2.5 hours). The mixture is concentrated *in vacuo*, the residue is recrystallised from carbon tetrachloride and 2.2 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-propionic acid are obtained having a melting point of 131°C.

d) 1.3 g of phosphorus pentachloride are added in portions at 0°C to a mixture of 1.9 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-propionic acid in 60 ml of diethyl ether and the mixture is stirred for three hours. The mixture is concentrated, the residue is recrystallised from benzene and 1.85 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-propionic acid chloride are obtained having a melting point of 111°C.

e) A solution of 0.7 g of trimethyl phosphite in 2 ml of diethyl ether is added dropwise at 0°C to a solution of 1.85 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-propionic acid chloride in 10 ml of diethyl ether. The mixture is left to stand for three days, concentrated *in vacuo* and 1.98 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-oxopropane-1-phosphonic acid dimethyl ester are obtained in the form of an oil.

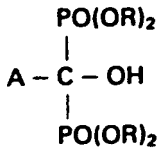
f) A solution of 1.98 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-oxopropane-1-phosphonic acid dimethyl ester in 15 ml of diethyl ether and 10 ml of dichloromethane is added dropwise at 0°C to a solution of 0.55 g of dimethyl phosphite and 50 mg of diethylamine in 10 ml of diethyl ether. The mixture is then stirred for three days at 0°C, the reaction mixture is worked up in customary manner, the residue is recrystallised from ethanol and 1 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) is obtained having a melting point of 131°C.

Example 22

0.34 g of iodotrimethylsilane is added at 0°C to a suspension of 0.22 g of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) in 4 ml of tetrachloromethane and the mixture is stirred for one hour at 0°C and for a further two hours at room temperature. The reaction mixture is then concentrated, the residue is recrystallised from ethanol and 130 mg of 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxypropane-1,1-diphosphonic acid are obtained having a melting point of 223°C.

CLAIMS

1. A diphosphonic acid derivative of the general formula



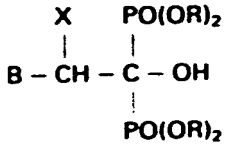
(I)

in which

R represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms, each R being the same or different, and

A represents the radical of an anti-inflammatorily and anti-phlogistically active carboxylic acid, ACOOH, which contains an aryl or heteroaryl group.

2. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ia)

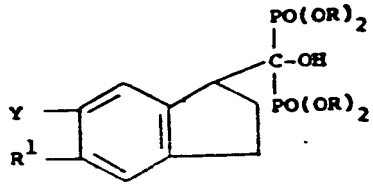
in which

R is as defined in claim 1,

X represents a hydrogen atom, a methyl group or an ethyl group, and

B represents a phenyl radical that is substituted in the *para*-position by an isobutyl radical, a cyclohexyl radical, an alkoxy radical or a 1-pyrrolinyl radical and, optionally, additionally substituted in the *meta*-position by a fluorine atom or a chlorine atom, or that is substituted in the *meta*-position by a benzoyl group or a phenoxy group, or that is substituted in the *ortho*-position by a 2,4-dichlorophenoxy group or a 2,6-dichlorophenylamino group.

3. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ib)

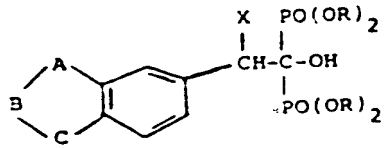
in which

R is as defined in claim 1,

R^1 represents a cyclohexyl radical or a cyclopentylmethyl radical, and

Y represents a hydrogen atom or a chlorine atom.

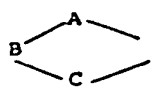
4. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ic)

in which

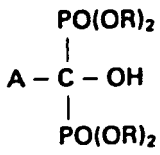
R and X are as defined in claim 1 and claim 2, respectively, and



represents the a radical selected from

CLAIMS

1. A diphosphonic acid derivative of the general formula



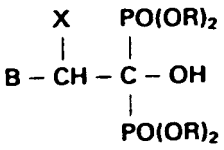
(I)

in which

R represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms, each R being the same or different, and

A represents the radical of an anti-inflammatorily and anti-phlogistically active carboxylic acid, ACOOH, which contains an aryl or heteroaryl group.

2. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ia)

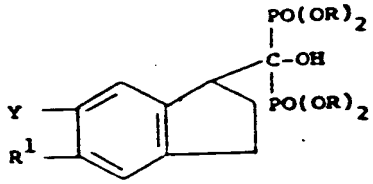
in which

R is as defined in claim 1,

X represents a hydrogen atom, a methyl group or an ethyl group, and

B represents a phenyl radical that is substituted in the *para*-position by an isobutyl radical, a cyclohexyl radical, an alkoxy radical or a 1-pyrrolinyl radical and, optionally, additionally substituted in the *meta*-position by a fluorine atom or a chlorine atom, or that is substituted in the *meta*-position by a benzoyl group or a phenoxy group, or that is substituted in the *ortho*-position by a 2,4-dichlorophenoxy group or a 2,6-dichlorophenylamino group.

3. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ib)

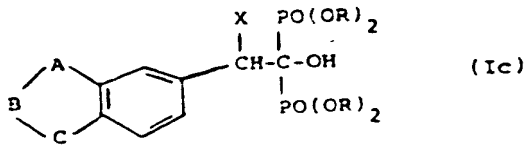
in which

R is as defined in claim 1,

R^1 represents a cyclohexyl radical or a cyclopentylmethyl radical, and

Y represents a hydrogen atom or a chlorine atom.

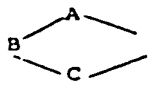
4. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



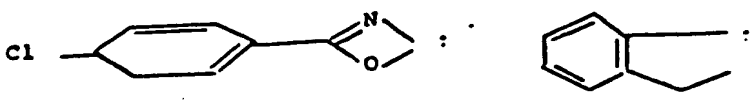
(Ic)

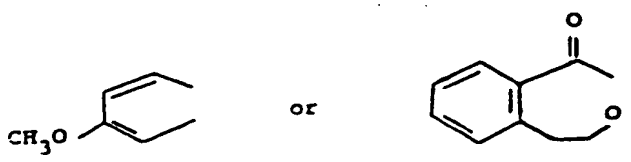
in which

R and X are as defined in claim 1 and claim 2, respectively, and

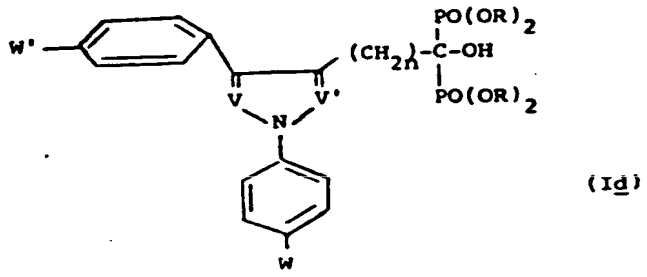


represents the a radical selected from





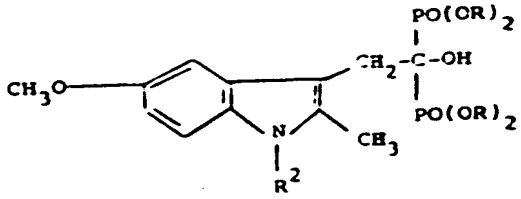
5. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Id)

in which
n is the number 1, 2 or 3,
R is as defined in claim 1,
W and W' are the same or different and each represent a hydrogen atom, a fluorine atom or a chlorine atom, and
one of the radicals V or V' represents a nitrogen atom and the other represents a methine radical which is unsubstituted or substituted by a phenyl group.

6. A diphosphonic acid derivative as claimed in claim 1, which is of the general formula



(Ie)

in which
R is as defined in claim 1, and
R_2 represents a *p*-chlorobenzoyl radical or a cinnamoyl radical.

7. A salt of a compound as claimed in any one of claims 1 to 6.

8. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 6.

9. A salt as claimed in claim 8, which is an alkali metal or alkaline earth metal salt.

10. A salt as claimed in claim 9, which is a sodium salt.

11. 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) or 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]-1-hydroxyethane-1,1-diphosphonic acid.

12. 2-(6-methoxy-2-naphthyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) or 2-(6-methoxy-2-naphthyl)-1-hydroxypropane-1,1-diphosphonic acid.

13. 2-(4-isobutylphenyl)-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) or 2-(4-isobutylphenyl)-1-hydroxypropane-1,1-diphosphonic acid.

14. 2-(11-oxo-2-dibenz[*b,f*]oxepinyl)-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) or 2-(11-oxo-2-dibenz[*b,f*]-oxepinyl)-1-hydroxyethane-1,1-diphosphonic acid.

15. (6-chloro-5-cyclopentylmethyl-1-indanyl)-hydroxymethanebis(phosphonic acid diethyl ester) or (6-chloro-5-cyclopentylmethyl-1-indanyl)-hydroxymethanediphosphonic acid.

16. 2-[2-(2,6-dichlorophenylamino)-phenyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) or 2-[2-(2,6-dichlorophenylamino)-phenyl]-1-hydroxyethane-1,1-diphosphonic acid.

17. 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid diethyl ester) or 2-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic

acid or the sodium salt thereof.

18. 2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethane-1,1-bis(phosphonic acid dimethyl ester) or 2-[3-(4-chlorophenyl)-1-phenyl-4-pyrazolyl]-1-hydroxyethane-1,1-diphosphonic acid.

19. 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxypropane-1,1-bis(phosphonic acid dimethyl ester) or 3-[4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolyl]-1-hydroxypropane-1,1-diphosphonic acid.

20. A process for the preparation of a diphosphonic acid derivative as claimed in claim 1, which comprises reacting an acyl phosphonate of the general formula

$$A-COPO(OR)_2 \quad \text{(II)},$$

in which R and A are as defined in claim 1, in the presence of a base with a phosphite of the general formula

$$HPO(OR)_2 \quad \text{(III)},$$

in which R is as defined in claim 1, and if desired, one or more of the following reactions are carried out in any appropriate order:

i) an ester is hydrolysed or converted into another ester;
ii) an acid or base is esterified
iii) a salt is converted into an acid or base or into another salt;
iv) an acid or base is converted into a salt.

21. A process as claimed in claim 20, which is carried out substantially as described in any one of Examples 1 to 22 herein.

22. A compound as claimed in claim 1, whenever prepared by a process as claimed in claim 20 or claim 21.

23. A salt as claimed in claim 7, whenever prepared by a process claimed in claim 20 or claim 21.

24. A physiologically tolerable salt as claimed in claim 8, whenever prepared by a process as claimed in claim 20 or claim 21.

25. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 6, 8 to 19, 22 and 24, in admixture or conjunction with a pharmaceutically suitable carrier.

26. A pharmaceutical preparation as claimed in claim 25, which is in unit dosage form.

27. A pharmaceutical preparation as claimed in claim 25 or claim 26, which is in a form suitable for enteral or parenteral administration.

28. A compound as claimed in any one of claims 1 to 6, 8 to 19, 22 and 24 or a preparation as claimed in any one of claims 25 to 27, for use in a method of treatment by therapy of a human or animal body.

29. A method of treating a human or animal body which comprises administering a compound as claimed in any one of claims 1 to 6, 8 to 19, 22, 24, 26 and 28 or a preparation as claimed in any one of claims 25 to 28 to the human or animal.

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